case has a growth response to folic acid been documented in the absence of other therapy, e.g. antibiotics for associated infections in sickle-cell disease or a gluten-free diet in cœliac disease.

Finally, it is worth while to review briefly the question of what effect, if any, folate deficiency has on the nervous system. Vitamin B_{12} deficiency is known to cause an organic neuropathy, and although the biochemical basis for this remains unknown, it is not generally considered that the mechanism for the neuropathy is the same as that for anæmia. Indeed, patients with vitamin B_{12} neuropathy may have little anæmia and often show high serum folate levels, while folic acid therapy aggravates, rather than improves, the neuropathy.

The various neurological syndromes that have been described in patients with folate deficiency or a defect of folate metabolism include: mental retardation associated with inborn errors of folate metabolism (Arakawa 1970, Tauro *et al.* 1976), a peripheral neuropathy or posterior lateral column lesion associated with nutritional folate deficiency, often in epileptics or the aged (Grant *et al.* 1965, Manzoor & Runcie 1976), brain and spinal cord damage associated with intrathecal methotrexate therapy (Kay *et al.* 1972), an organic dementia associated with nutritional folate deficiency in the elderly (Strachan & Henderson 1967), a schizophrenia-like illness associated with homocystinuria in a child with an inborn error of folate metabolism (Freeman *et al.* 1975), and an impaired psychological state with relative protection from fits associated with folate deficiency in epileptics (Reynolds 1973). The extensive literature on all these aspects has recently been comprehensively reviewed by Reynolds (1976) and the reader is referred to that article for an excellent survey of this subject.

The best substantiated of these effects is the neurological damage caused by methotrexate. Whether nutritional folate deficiency, even when severe, causes more than minor psychological changes remains an open question. Double-blind trials have not shown that folate therapy increases fit frequency in epilepsy, while a cause-and-effect relation has not yet been satisfactorily demonstrated between nutritional folate deficiency and organic neurological damage. Moreover, the suggestion that methyltetrahydrofolate may be involved in the brain in the methylation of catecholamines and indole-amines (Leysen & Laduron 1974) has not been confirmed as a physiological pathway (Meller *et al.* 1975). S-adenosylmethionine remains the most likely methyl donor in the brain and, as yet, no special important role for folate in the central nervous system has been proven.

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Nonscorbutic Effects of Vitamin C Deficiency: Clinical Aspects

In scurvy produced experimentally, the more complete the dietary deficiency of vitamin C the more quickly the first signs of scurvy present themselves (Crandon *et al.* 1940, Hodges *et al.* 1969). Scurvy observed clinically generally presents as part of a mixed deficiency.

Russell *et al.* (1968) have suggested that low vitamin status may play a part in maintaining

upper gastrointestinal tract hæmorrhage which had been initially precipitated by 'aspirin' or 'alcohol'. Royston's sign is now thought by him not to be specific of vitamin C deficiency (Royston 1976, personal communication). Taylor has postulated that senile 'purpura' and sublingual 'petechiæ' may be caused by lack of vitamin C (Taylor 1966). The former condition was shown as long ago as 1950 by Tattersall & Seville not to be associated with low vitamin C levels, and this lack of association has been subsequently confirmed by white-cell estimations by Andrews & Brook (1966). Sublingual 'petechiæ' have been in fact shown to be aneurysmal dilatations of venules and also not associated with vitamin C deficiency (Andrews *et al.* 1969).

Patients with iron overload tend to have a reduced concentration of white-cell vitamin C, and iron-deficient patients a higher level than normal (Jacobs *et al.* 1971). Andrews *et al.* (1967) in a study of the use of total dose infusion of iron dextran, had found in the patients studied that those with iron deficiency had slightly higher levels of white-cell vitamin C than the controls. Asquith *et al.* (1967) have reported a case of reticulocyte response and a resolution of anæmia in a patient with scurvy, purely as a result of administering a high dosage of vitamin C, the patient remaining on a folate-deficient diet. In this connexion, Stokes *et al.* (1975) suggest that vitamin C has an important role in preventing the oxidation of tetrohydrofolate, thus keeping the folate metabolic pool available. Blood loss in scurvy can obviously cause anæmia, and the multifactorial etiology of this has been reviewed in detail by Cox (1968).

Andrews *et al.* (1966) reported that there was a considerable seasonal fall of vitamin C levels during the winter months, both in young and old subjects. Allen *et al.* (1967) showed that there is a sex difference in vitamin C white cell levels. Tetracycline has been shown to lower these levels, first by Shah *et al.* (1968), confirmed later by Windsor *et al.* (1972). Oral administration of vitamin C in the treatment of pressure sores has been shown to increase collagen formation (Burr & Rajan 1972).

Groups Characterized by Low Vitamin C Levels

Low total white-cell levels have been found in various groups, in whom they can be raised to those of normal young adults by supplementation. This suggests that the causes are due to low intake rather than multiple pathology; however, the low intake may be caused on occasion by gastrointestinal pathology (Cohen & Duncan 1967).

The elderly: This was shown by Bowers & Kubik (1965) and confirmed by Andrews *et al.* (1969).

The institutionalized: In the elderly, low vitamin C levels were first described by Kataria *et al.* (1965) and confirmed a year later by Andrews & Brook (1966). In the young, Dawson & Duncan (1975), when investigating the effect of anticonvulsants in institutionalized children and adolescents, found that significantly lower levels were present in the institutionalized, whether on anticonvulsants or not, compared in young adults.

Low levels found in the institutionalized were considered by Andrews (1973) to be due to an inadequate supply of fruit and fruit juices; the effect of institutionalized cooking on such ingredients as potatoes, which form a large source of dietary vitamin C; and the delay in delivery of food to the patient or resident.

Smokers: Brook & Grimshaw (1968) showed that smokers had lower levels of vitamin C in white cells as compared with nonsmokers, and Pelletier (1970) showed that smokers' levels of blood vitamin C could be brought to those normally found in nonsmokers by supplementation with large doses of ascorbic acid. The reasons for these findings still remain unclear.

Significance of Low Biochemical Levels

In the absence of clinically recognizable scurvy, it remains unproven that low blood levels of vitamin C are deleterious to man, but this should be a matter for concern. Williams & Deason (1967) showed a considerable variation in the vitamin C requirements of experimental animals, and this could well apply in man.

Further Research Needed

There is a great need for further research into vitamin C deficiency in man, and such programmes might include the investigation of:

(1) Mental changes: Walker (1968) first reported that certain mental changes, including depression, could well be associated with such a deficiency. In a study of experimentally induced scurvy, Kinsman & Hood (1971) observed personality changes.

(2) The relation of vitamin C deficiency to folate deficiency: It is unfortunate that Hodges *et al.* (1969) did not apparently perform red cell and serum folate estimations during their work on experimental scurvy, so that an important gap in our knowledge remains. It would be particularly interesting to know these values in such a situation, especially in view of the work of Stokes *et al.* (1975) referred to previously.

(3) The renal threshold of vitamin C excretion: A renal zone rather than a renal threshold was postulated by Ahlborg in 1946 in his study on students. The work of Davies *et al.* (1976) reinforces the importance of carrying out this type of research in subjects of various ages, including the elderly as advocated by Andrews (1968).

(4) Longitudinal studies of vitamin C total white cell levels in the institutionalized: As at least

5–10% of patients admitted to geriatric departments remain in long-term hospital care (Andrews 1976, unpublished) such an investigation would be relatively easy to perform. It would be of considerable practical value in elucidating the true significance of low vitamin C white-cell levels found in the institutionalized.

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Nonscorbutic Effects of Vitamin C: Biochemical Aspects

The Ascorbic Acid Molecule

The role of vitamin C (L-xyloascorbic acid, ascorbic acid, AA) in correcting the biochemical lesion of scurvy is reasonably well established. It is required for the proper hydroxylation of collagen lysine and proline; without a sufficiency of AA, collagen formation is impaired (Barnes & Kodicek 1972). Defective formation of collagen could, in the final analysis, account for most – but possibly not all – of the characteristics of classical scurvy.

A collagen-like amino-acid sequence is a characteristic of at least two other structures in the body, namely the $C1_q$ subcomponent of complement (Reid 1974) and the basement membrane (Kefalides 1973). It is conceivable therefore that at least some of the so-called 'extra-antiscorbutic' involvements of AA will prove, in the final analysis, to be explicable in terms of a mechanism not entirely unrelated to the currently accepted mode of action of AA in preventing classical scurvy.

AA is not biologically specific in this respect. Recent studies have shown that iso-AA (D-araboascorbic acid) has an equivalent capacity to prevent scurvy; earlier claims that it possessed only a fraction of the antiscorbutic potency of AA were based on studies where a satisfactory level of iso-AA had not been attained in the tissues (Hughes 1973). AA, after oxidation to dehydroascorbic acid, crosses biological membranes with facility, and most tissues contain a glutathione-based system by which dehydroascorbic acid is reduced back to AA (Hughes 1964, Grimble & Hughes 1967). These mechanisms ensure that ingested AA is quickly absorbed and enters the tissues. In biochemical terms, the AA molecule possesses considerable biochemical versatility (Lewin 1974); theoretically, its properties as a biological reductant could be of significance in maintaining the integrity of tissue thiol (—SH) groups, thereby modifying a whole range of biochemical happenings. In terms of availability, distribution and properties the AA molecule is therefore endowed with considerable potential for involvement in areas other than the simple prevention of scurvy.

Extra-antiscorbutic Involvements

There are indications that the prevention of scurvy – as traditionally defined – is not the only involvement of AA in the mammalian body. Tetrahydrofolic acid, which has 43% of the activity of AA in